REMARKS

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Reconsideration and allowance of the subject application are respectfully requested.

Claims 1-17, 20, 24-29, 31-34, and 38-47 are pending in the application.

The rejection of claims 1-18, 20, 24-34, and 38-46 under 35 U.S.C. § 112, first paragraph, is respectfully traversed. Original claim 23 recites ("room temperature (20°C), preferably below this"), which provides clear basis for the term "below 20°C." No new issues or new matter were added. Applicant reserves the right to pursue this subject matter. This rejection is obviated by the amendment set forth above to claims 1 and 27 to recite "of 20 °C or less." Accordingly, withdrawal of the Section 112 rejection is respectfully requested.

Applicant notes that the rejection of claims 1-4, 7, 10, 11, 13, 15, 22 and 27 under 35 U.S.C. § 102(e) as being anticipated by U.S. Patent No. 5,858,410 (Muller '410) has been withdrawn in light of a previous amendment now reversed in part by the amendment to the claims set forth above. Applicant submits that the claimed invention is not anticipated by Muller '410 for the reasons of record and for the following reasons.

Applicant respectfully requests that the Examiner properly distinguish between:

1. Teachings in the prior art on how to <u>produce</u> the particles using a high pressure homogenization medium; and
2. Teachings in the prior art on how to <u>use</u> the already produced particles in solvents, such as organic solvents.

Teachings on how to <u>use</u> the already produced particles are very different from teachings on how to <u>produce</u> the partcles in the first place and these teachings are not interchangeable.

The claimed process for gentle preparation of superfine micro- and nanoparticles of a solid particle matrix material requires use of "an anhydrous or water-reduced dispersion medium containing less than 50 wt.% of water" as a high pressure homogenization medium in a piston-gap homogenizer to produce the particles. [See claims 1, 27, 46 and 47.]

As discussed in detail below, the entire specification of Muller '410 requires the use of a large amount of water (about 80 to 99 % of water) as the high pressure medium in order to create cavitation and produce the particles. Muller '410 also teaches away from using lesser amounts of water, as discussed more fully below. Applicant respectfully submits that the Examiner has not properly and fairly considered these teachings.

As discussed in detail below, the claims of Muller '410 recite using an "organic solvent" to dissolve the already produced particles. This teaching relates to use of the already produced particles. Furthermore, this teaching on how to use the particles cannot be construed as a teaching for producing the particles.

The entire specification of Muller '410 teaches to use a large amount of water as the high pressure homogenization medium.

Muller '410 teaches that the "dispersion principle is cavitation." See column 4, lines 6-7 of Muller '410. Cavitation by definition requires a large amount water. At column 5, lines 27-28 that "Suspensions were prepared with a drug, which was ground in an air jet, in an aqueous surfactant solution." [Emphasis added.] The specification of Muller '410 in fact teaches that the high pressure dispersion medium is water or an aqueous medium containing about 80 to 99 % of water, which is in a direction away from the claimed invention. There is no disclosure of using a non-aqueous high pressure homogenization medium or of a water reduced (less than

about 50% of water) high pressure homogenization medium. In this respect, see the complete specification and in particular all of the examples of Muller '410.

In some examples of Muller '410, glycerol is used for serving as an emulsion stabilizer. However, glycerol cannot be considered as a organic solvent medium for high pressure homogenization and its content in all cases is below 16.7%. All other components used are solids (such as mannitol and phospholipon). Mannitol is introduced in form of an aqueous solution. So that there is no organic solvent at all.

For these reasons alone, Muller '410 cannot anticipate the claimed invention.

The claims of Muller '410 do not teach using an organic solvent as the high pressure medium to produce the particles.

The only mention of a non-aqueous medium (organic solvent) in Muller '410 is in the claims. However, the organic solvent is for dispersing the product particles of claim 1. In other words, the organic solvent is for using the already produced particles, and not as the high pressure homogenization medium for producing the particles. There is no disclosure to the contrary in Muller '410.

For example, claim 1 of Muller '410 recites a process for the preparation of a drug carrier comprising "a therapeutically active compound, which is insoluble, only sparingly soluble or moderately soluble in water, aqueous media and/or organic solvents, wherein said active ingredient is solid at room temperature ..., when introduced into water, aqueous media and/or organic solvents, the active compound has an increased saturation solubility and an increased rate of dissolution compared with powders of the active compound prepared using an ultrasonic probe, a ball mill or a pearl mill, said solid particles having been comminuted… by using a piston-gap homogenizer."

Thus, claim 1 of Muller '410 refers to the solubility of the active ingredient in water, aqueous media and/or organic solvents and the increased saturation solubility and increased rate of dissolution when introducing the already prepared micro- and nanoparticles into organic solvents. The same reference is in other claims. The only link in the entire document to organic solvents is in the claims but without any

reference to a consideration of using the organic solvent as the high pressure homogenization medium to produce the particles.

In addition, in Example 7 of Muller '410 it is clearly mentioned that for testing the saturation solubility of the produced particles a **"dispersion medium"** was determined after removing the liquid medium of the produced nanosuspensions. This fits to the subject-matter of claims of Muller '410 and demonstrates that there is indeed a difference between the "dispersion media" of those claims and the "high pressure homogenization medium" used for preparation of the nanosuspensions. The same has been made in Example 8 of Muller '410 for determination of the dissolution properties.

On page 7 of the Office Action, in regards to claim 1 of Muller '410, the Examiner states, "the claim [1 of Muller '410] recites 'wherein said particles are dispersed in a non-aqueous medium', if Applicant alleges that said medium is not the homogenization medium, then why Applicant does not cited or show what did the homogenization medium include?" Applicant has responded to this question fully above. As shown above, Muller '410 teaches that the homogenization medium for preparing the particles using cavitation is without doubt water or an aqueous medium containing about 80 to 99 % of water, whereas the organic solvent in the claims of Muller '410 is only referring to dissolving the already prepared particles.

In sum, there is simply no disclosure in Muller '410 teaching or suggesting to use a non-aqueous or water reduced (less than 50 % of water) high pressure homogenization medium. Any statement to the contrary lacks support.

In view of the differences between the claimed invention and Muller '410, withdrawal of the Section 102 rejection is respectfully requested.

The rejection of claims 1-20 and 22-47 under 35 U.S.C. § 103 as being unpatentable over WO 98/14174 (Desai) in view of Muller is respectfully traversed. The claimed invention is not obvious over the theoretical combination of Desai in view of Muller for the reasons of record and for the following reasons.

As discussed above, Muller '410 teaches away from the claimed invention by requiring a large amount of water (80 to 99 % of water) to provide cavitation and

produce the particles.

As discussed below, Desai also teaches away from the claimed invention by requiring the use of a large amount of water (over 80%) to produce the particles.

Since both Muller '410 and Desai teach to use far greater than 50% water in the homogenization medium to produce the particles, the combination of certainly must teach or suggest such. For this reason alone, the Section 103 rejection should be withdrawn.

Desai discloses a process for the preparation of a water insoluble drug for in-vivo delivery. Desai's method comprises as step 1 the dissolution of the drug in an organic solvent to form a drug loaded organic phase, as step 2 the **addition of water** to form an aqueous phase, and as step 3 the high pressure homogenization to form an **emulsion** from the organic phase and the aqueous phase. As further optional steps there are the evaporation of the organic solvent and the removal of the water for recovering the micro- or nanoparticles as such in a dry and re-dispersible form.

Thus, Desai uses throughout the entire disclosure thereof and without exception for high pressure homogenization a medium comprising an organic phase **and an aqueous phase**, i.e., an emulsion. [See claims 1 and 26, and the specification of Desai at page 10, lines 12 to 21, page 12, lines 15 to 25, page 14, lines 13 to 24, page 17, line 31 to page 18, line 7, and all Examples.] There is no disclosure Desai to use **only** an organic solvent as high pressure homogenization medium or a high pressure homogenization medium containing **less than about 50 % of water.**

The Examiner is correct in stating that the drug is **dissolved** in an organic solvent as a first step and that subsequently albumin is added. **However, Desai also requires the additional step of adding the aqueous phase before homogenization.** The albumin as such has the function of a stabilizer and according to the disclosure of Desai it is added in the form of a serum albumin solution. All Examples of Desai use such a serum albumin solution and also an aqueous phase, which aqueous phase in turn is indeed the major component of the

medium used for high pressure homogenization and is present in an amount of at least 80 % (v/v) and usually over 90 % (v/v). [See the Examples of Desai.] Thus, Applicant respectfully submits that the Examiner is incorrect in stating or assuming that Desai disclose a process using only an organic solvent or a water-reduced medium containing less than 50 % water as high pressure homogenization medium. The Examiner improperly ignores the required water addition prior to homegenization.

Again, the use of methylene chloride, chlorform and/or ethanol is just the initial step of Desai's process to prepare a solution of the drug forming an organic phase to which in the second step the aqueous phase in form of a serum albumin solution is added as major component for completing the mixture to be high pressure homogenized. The subsequent homogenization for 5 minutes at low RPM in a Vitris homogenizer, model Tempest I.Q. in order to form a crude emulsion cited by the Examiner is **not high pressure homogenization** but just an initial pre-mixing of the drug/organic phase/aqueous phase. As mention further in the Example, if read carefully, thereafter this crude emulsion is transferred into a high pressure homogenizer wherein the relevant high pressure homogenization takes place.

The Examiner's reference to the dispersion of taxol in ethanol without water according to Example 4 is misleading. This is only the initial step of the overall process of Desai and does not at all refer to the high pressure homogenization step. As one can see from Example 4 when reading further on there is the addition of 29.4 ml of a surfactant solution (1 % w/v) (constituting the aqueous phase) to the 0.6 ml chloroform/ethanol/taxol mixture constituting the organic phase. Thus, the water content is indeed 98%. Only this mixture of organic and aqueous phases is high pressure homogenized.

As outlined above, the disclosure of Desai differs from the presently claimed subject matter in that Desai uses water or an aqueous medium containing a high amount of water, i.e., more than about 50 % of water, and that Desai does not disclose use of a piston-gap homogenizator.

Desai actually teaches away from the claimed invention by teaching to have a water content as high as possible. In this respect, see Example 7 on page 38 of

Desai, which deals with the effect of the phase fraction of organic solvent on the particle size, keeping in mind that it is the object to prepare particles suitable for intravenous injection and thus particles which should be as small as possible. Example 7 discloses the importance of having an unusually low phase fraction of the organic solvent in the system. It mentions that an increase of the phase fraction lead to a significant increase in particle size, or in other words, the particle size obtainable is smaller if the water content of the homogenization medium is higher. Considering this, there is the clear recommendation to have a low organic phase fraction. This fits to the knowledge that the occurrance of cavitation will decrease with a decreasing water content. Such a decrease is to be avoided. Since it is the object of Desai to use a high comminution effect to produce small particle sizes using a large amount water in the homogenization medium, the skilled person will not reduce the water content of the high pressure homogenization medium. Prior to the present invention, those skilled in the art knew that water or substantially water is the only medium of choice for high pressure homogenization to provide cavitation effects.

Mulluer '410 does not provide the deficiencies of Desai. Muller '410 also does not teach or suggest using an anhydrous or water-reduced dispersion medium containing less than 50 wt.% of water. Like Desai, Muller '410 teaches to use water or predominately water. Thus, the combination of Desai and Muller '410 teaches in a direction away from the claimed invention, i.e. higher amounts of water in the high pressure dispersion medium.

The clamed invention exhibits unexpected results.

It is indeed surprising that use of a piston-gap homogenizer in combination with high pressure homogenization medium having a dramatically reduced content of water (making it a minor component of the medium) or even with no water content and thus resulting in a dramatically decreased cavitation effect or only a minimized degree of cavitation effect up to no cavitation effect, still results in the preparation of micro- and nanoparticles presently described having an average diameter in the number distribution of 5.6 µm or less and in particular of less than 1 µm.

This is even more surprising in light of Desai and Muller '410 teaching the opposite-the higher the water content the higher the comminution is, which in turn is desired. Thus, in contrast to Desai and Muller '410, it has been surprisingly found that a considerably reduced water content does not affect the particle size reduction. An explanation for this is that there must be an effect different from cavitation, which results in the observed particle size reduction.

In view of the many differences between the claimed invention and the theoretical combination of Desai and Muller, and the unexpected advantages of the claimed invention, with drawal of the Section 103 rejection is respectfully requested.

In view of all of the rejections of record having been addressed, Applicants submit that the claimed invention is in condition for allowance and Notice to that effect is respectfully requested.

Respectfully submitted,
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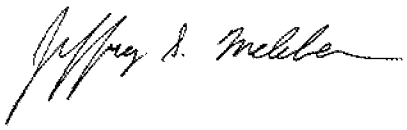

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